(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 895 989 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
10.02.1999 Bulletin 1999/06

(21) Application number: **98306198.7**

(22) Date of filing: **04.08.1998**

(51) Int Cl 6: **C07D 207/08**, C07D 211/22, C07D 295/112, C07D 265/30, C07D 221/20, C07D 207/27, C07C 211/05, C07C 211/06, C07C 211/58, C07C 275/30, A61K 31/445, A61K 31/545, A61K 31/13, A61K 31/135

(84) Designated Contracting States.
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States.
AL LT LV MK RO SI

(30) Priority: **07.08.1997 US 54952 P**

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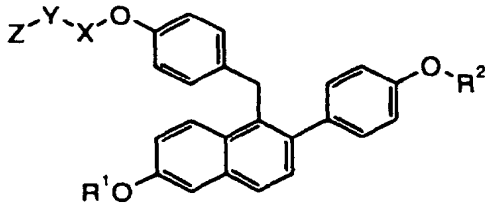
(54) 1-[4-(Substituted alkoxy)benzyl] naphthalene compounds having estrogen inhibitory activity

(57) A class of substituted benzylnaphthylene compounds of the structure



where R^1 and R^2 are independently hydrogen, alkyl of one to six carbon atoms, acyl of two to six carbon atoms, or phenacyl; X is $-(CH_2)_{1-6}$; Y is absent or is selected from 1,4-piperazinylene; ureido; N-(lower alkyl)ureido; N'-(lower alkyl)ureido; or N, N'-(di-lower alkyl ureido; and Z is 1-, 2- or 3-pyrrolidinyl; 1-, 2-, or 3-[1-(lower alkyl) pyrrolidinyl]; 1-2-,3- or 4-piperidinyl, 1-, 2-, 3- or 4-[1-lower alkyl)piperidinyl]; N,N-dialkyl; 1-azepinyl; 1- or 2-naphthylamino, 4-morpholinyl, dimethyl-4-morpholinyl, 3-azaspiro[5.5]undecan-3-yl; pyrrolidinon-1-yl; unsubstituted phenyl; or phenyl substituted with acyl of two to four carbon atoms, alkyl of one to four carbon atoms, halo, or alkoxy of one to four carbon atoms; with the proviso that n is not 2 or 3 when Z is 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, N,N-dimethylamino or N,N-diethylamino; are selective estrogen receptor modulators useful in the prophylaxis or treatment of breast cancer.

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Printed by Jouve, 75001 PARIS (FR)

[0011] Y is absent or is selected from the group consisting of 1,4-piperazinylene, ureido, N-(lower alkyl)ureido; N'-(lower alkyl)ureido; and N, N'-(di-lower alkyl ureido

[0012] The substitutent Z is selected from the group consisting of 1-, 2- or 3-pyrrolidinyl; 1-, 2-, or 3-[1-(lower alkyl) pyrrolidinyl]. 1- 2-,3- or 4-piperidinyl: 1-, 2-, 3- or 4-[1-lower alkyl)piperidinyl]; N,N-dialkyl in which the alkyl groups are independently from one to four carbon atoms; 1-azepinyl. 1- or 2-naphthylamino, 4-morpholinyl; dimethyl-4-morpholinyl, 3-azaspiro[5.5]undecan-3-yl; pyrrolidinon-1-yl; unsubstituted phenyl; and phenyl substituted with one or two groups independently selected from acyl of two to four carbon atoms, alkyl of one to four carbon atoms halo, and alkoxy of one to four carbon atoms

[0013] All of the above definitions are with the proviso that n is not 2 or 3 when Z is 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, N,N-dimethylamino or N,N-diethylamino.

[0014] In a second embodiment, the present invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound as defined above in combination with a pharmaceutically acceptable carrier

[0015] In another embodiment, the present invention comprises a method of treating or inhibiting estrogen-dependent cancers in women, particularly cancer of the breast and uterus, comprising administering to a woman in need of such treatment an effective amount of a compound as defined above.

[0016] As used throughout this specification and the appended claims, the following terms have the meanings ascribed to them.

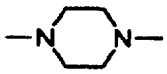
[0017] "Alkyl of one to six carbon atoms" means a univalent radical derived by the removal of one hydrogen atom from methane, ethane, or a straight or branched hydrocarbon of three to six carbon atoms and is typified by methyl, ethyl, *n*- or *iso*-propyl, *n*-, *sec*- *iso*- or *tert*-butyl, *n*-pentyl, 2-methylbutyl, *n*-hexyl, 2-methylpentyl, 2,3-dimethylbutyl, and the like.

[0018] "Acyl" denotes an alkyl group as defined above, attached to the parent molecular moiety through a carbonyl group.

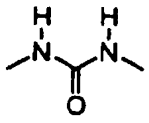
[0019] "Lower alkyl" denotes an alkyl group as defined above containing one to four carbon atoms.

[0020] The term "alkoxy" refers to an alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom.

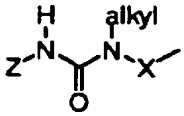
[0021] The term "1,4-piperazinylene" denotes a divalent radical of the structure



and the term "ureido" means the divalent radical represented by the structure



[0022] The term "N-(lower alkyl)ureido", as used herein, means a ureido group in which the lower alkyl group is attached to the nitrogen nearest the group denoted "X" in structure **1** above, thus:



and "N'-(lower alkyl)ureido" means a ureido group in which the lower alkyl group is attached to the nitrogen nearest the group denoted "Z" in structure I above, thus.

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(piperidin-2-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(piperidin-3-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(piperidin-4-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(piperidin-2-yl)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(piperidin-3-yl)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(piperidin-4-yl)propoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(piperidin-1-yl)butoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(piperidin-2-yl)butoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(piperidin-3-yl)butoxy)benzyl]naphthalene; and
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(piperidin-4-yl)butoxy)benzyl]naphthalene.

[0028] Compounds of the present invention in which Y is absent and Z is azepinyl include:

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(azepin-1-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(azepin-2-yl)methoxybenzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(azepin-3-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(azepin-4-yl)methoxybenzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(azepin-2-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(azepin-3-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(azepin-2-yl)propoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(azepin-3-yl)propoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(azepin-1-yl)butoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(azepin-2-yl)butoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(azepin-3-yl)butoxy)benzyl]naphthalene; and
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(azepin-4-yl)butoxy)benzyl]naphthalene.

[0029] Compounds of the present invention in which Y is absent and Z is 4-morpholinyl include:

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(morpholin-4-ylmethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[(4-(4-(morpholin-4-yl)butoxy)benzyl]naphthalene.
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(5-(morpholin-4-yl)heptoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(morpholin-4-yl) hexoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2,6-dimethylmorpholin-4-ylmethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(2,6-dimethylmorpholin-4-yl)ethoxy)benzyl]naphthalene; and
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(2,6-dimethylmorpholin-4-yl)propoxy)benzyl]naphthalene.

[0030] Compounds of the present invention in which Y is absent and Z is 1- or 2-aminonaphthyl include

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(naphth-1-ylamino)methoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(naphth-1-ylamino)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(naphth-1-ylamino)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(naphth-1-ylamino)butoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(naphth-2-ylamino)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(naphth-2-ylamino)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(naphth-2-ylamino)propoxy)benzyl]naphthalene; and
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(naphth-2-ylamino)butoxy)benzyl]naphthalene.

[0031] Compounds of the present invention in which Y is absent and Z is 3-azaspiro[5.5]undec-3-yl include:

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-azaspiro[5.5]undec-3-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(3-azaspiro[5 5]undec-3-yl)ethoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(3-azaspiro[5.5]undec-3-yl)propoxy)benzyl]naphthalene, and
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(3-azaspiro[5.5]undec-3-yl)butoxy)benzyl]naphthalene.

[0032] Compounds of the present invention in which Y is absent and Z is 2,3,5,6-tetrahydro-2,6-dioxo-1,3-dimethyl-1*H*-purin-8-yl include:

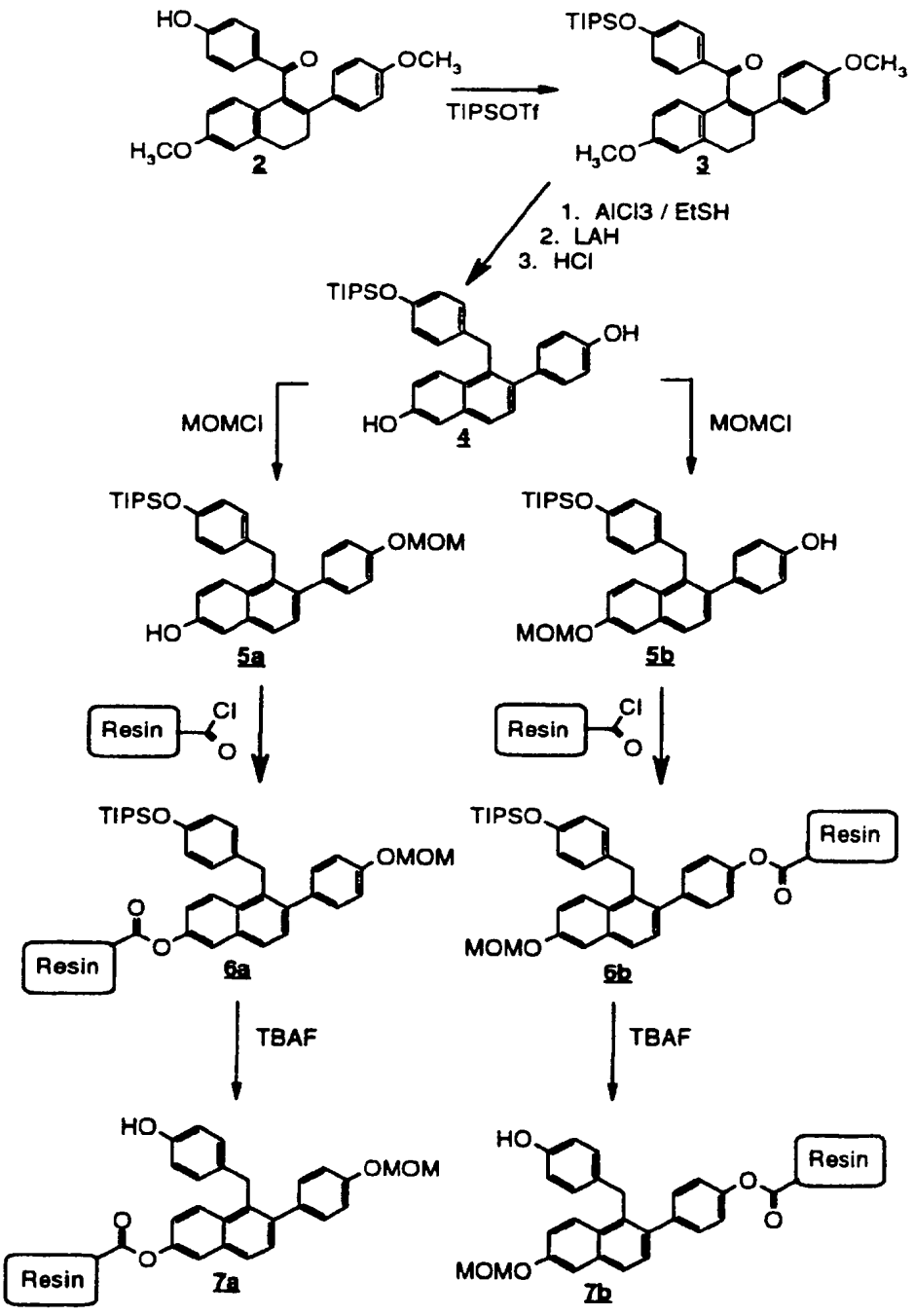
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2,3,5,6-tetrahydro-2,6-dioxo-1,3-dimethyl-1*H*-purin-8-yl)methoxybenzyl]

N-methyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-methylphenyl urea;
N-methyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-chlorophenyl urea;
N-methyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-hydroxyphenyl urea;
N-methyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-methoxyphenyl urea.
N-methyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-3-chloro-2-methylphenyl urea;
N-methyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-methylphenyl urea;
N-methyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-chlorophenyl urea;
N-methyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-hydroxyphenyl urea;
N-methyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-methoxyphenyl urea;
N-methyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-3-chloro-2-methylphenyl urea;
N-methyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-methylphenyl urea;
N-methyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-phenyl urea;
N-methyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-chlorophenyl urea;
N-methyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-hydroxyphenyl urea.
N-methyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-methoxyphenyl urea;
N-methyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-3-chloro-2-methylphenyl urea;
N-ethyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-methylphenyl urea;
N-ethyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-chlorophenyl urea;
N-ethyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-hydroxyphenyl urea;
N-ethyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-methoxyphenyl urea;
N-ethyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-3-chloro-2-methylphenyl urea;
N-ethyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-methylphenyl urea;
N-ethyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-chlorophenyl urea;
N-ethyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-hydroxyphenyl urea;
N-ethyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-methoxyphenyl urea;
N-ethyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-3-chloro-2-methylphenyl urea;
N-ethyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-methylphenyl urea;
N-ethyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-phenyl urea;
N-ethyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-chlorophenyl urea;
N-ethyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-hydroxyphenyl urea;
N-ethyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-methoxyphenyl urea, and
N-ethyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-3-chloro-2-methylphenyl urea.

[0036] Examples of compounds of the present invention where Y is N'-alkylureido and Z is phenyl or substituted phenyl include:

N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-methyl-N'-phenyl urea;
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-methyl-N'-phenyl urea;
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-ethyl-N'-phenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-methyl-N'-4-methylphenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-methyl-N'-4-chlorophenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-methyl-N'-4-hydroxyphenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-methyl-N'-4-methoxyphenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-methyl-N'-3-chloro-2-methylphenyl urea,
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-ethyl-N'-4-methylphenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-ethyl-N'-4-chlorophenyl urea,
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-ethyl-N'-4-hydroxyphenyl urea,
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-ethyl-N'-4-methoxyphenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-ethyl-N'-3-chloro-2-methylphenyl urea;
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-methyl-N'-4-methylphenyl urea;
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-methyl-N'-4-chlorophenyl urea;
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-methyl-N'-4-hydroxyphenyl urea;

Reaction Scheme 1

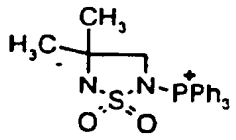


[0041] The mixture of isomers, **5a** and **5b** are next reacted with the acid chloride form of the resin to attach the both triisopropylsilyl protected isomers to the resin backbone.

This process is carried out in an aprotic organic solvent, such as dichloromethane, by reacting the acid chloride form of the resin with the protected alcohol mixture in the presence of an amine acid scavenger such as triethylamine The reaction is typically carried out by gently stirring the mixture (to avoid mechanical breakage of the resin beads) at room temperature for a period of from 8 to 24 hours. The loaded resin, **6a** and **6b** is then collected by filtration and washed free of the unreacted substrate

[0042] Deprotection of the mixture, **6a** and **6b** with tetra-*n*-butylammonium fluoride in tetrahydrofuran, using the method of S. V. Frye, Tetrahedron Lett., **27**. 3223 (1986) removes the triisopropylsilyl protecting group and yields the mixture of resin-bound, deprotected isomers **7a** and **7b**

[0043] The mixture of resin-bound intermediates, **7a** and **7b**, is next derivatized at the free hydroxyl position by reaction of the free phenolic functions of **7a** and **7b** with a commercially available alcohol, ZYX-OH, under Mitsunobu conditions (see J L Castro, *et al*, J. Org. Chem., **59**· 2289-2291 (1994). These couplings were carried out by combinatorial chemistry means by placing 30 mg (0.04 mmol of the mixture of resin-bound phenolic substrates **7a** and **7b** in each well of a 96-well plate, together with 0 4 mL of a 1 molar solution of the particular alcohol in toluene. To each well was also added 0 4 mL of a 1 molar suspension of a betaine coupling reagent having the structure



[0044] The derivatized, resin-bound mixture of intermediates **8a** and **8b** are then subjected to cleavage by reaction with n-propylamine at room temperature for a period of about 24 hours to produce the methoxymethyl protected compound mixture **9a** and **9b**.

[0045] In the instances where the desired end-product is a 6-hydroxy-2-(4-hydroxyphenyl)naphthalene of structure **1a** where both R^1 and R^2 are hydrogen, the methoxymethyl protecting groups of **9a** and **9b** are removed by reaction with acid, typically a trace of 4 molar hydrochloric acid in dioxane, according to the method of J. Auerbach, *et al.*, J. Chem Soc., Chem Commun, 298 (1974)

[0046] The compounds of structure **1b** in which the groups designated R^1 are both the same can be prepared directly from **1a** by ether-forming or esterification reactions well known in the art

[0047] Referring to Reaction Scheme 2 in the instance where the desired end product of the reaction is a compound of structure **1e** in which R^1 is alkyl, alkylcarbonyl, or phenylcarbonyl, compound mixture **9a** and **9b** is first separated by conventional means such as column chromatography. Compound **9a** is then reacted under basic conditions to produce the desired methoxymethyl protected ether or ester, **1c**, followed by cleavage of the methoxymethyl protecting group to yield the desired product, **1e**.

[0048] In a similar fashion, if the desired end-product is a compound of structure **1f** where R^2 is is alkyl, alkylcarbonyl, or phenylcarbonyl, compound **9b** (separated from its isomer) is reacted under basic conditions to produce the desired methoxymethyl protected ether or ester, **1c**, followed by cleavage of the methoxymethyl protecting group to yield the desired product, **1f**

[0049] Specifically, when is it desired that R^1 be alkyl, compound **9** is reacted with a suitable base such as potassium

of forming acid addition salts with a wide variety of organic and inorganic acids and include the physiologically acceptable salts which are often used in the pharmaceutical formulation art The present invention contemplates within its scope pharmaceutically acceptable acid addition salts of compound of structure 1

[0054] The term "pharmaceutically acceptable salts" denotes salts of the type described by S. M Berge, *et al.*, J. Pharm. Sci., **66**(1) 1-19 (1977) and includes typical inorganic acids such as hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, phosphoric, hypophosphoric and the like. Salts derived from organic acids, such as aliphatic mono and dicarboxylic acids, phenyl substituted alkanoic acids, hydroxyalkanoic and hydroxyalkandioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, may also be used

[0055] Such pharmaceutically acceptable salts include the acetate, phenylacetate, trifluoroacetate, acrylate, ascorbate, benzoate, chlorobenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, methylbenzoate, o-acetoxybenzoate, naphthalene-2-benzoate, hydrobromide, isobutyrate, phenylbutyrate, β-hydroxybutyrate, butyne-1,4-dioate, hexyne-1,4-dioate, caprate, caprylate, hydrochloride, cinnamate, citrate, formate, fumarate, glycollate, heptanoate, hippurate, lactate, malate, maleate, hydroxymaleate, malonate, mandelate, mesylate, nicotinate, isonicotinate, nitrate, oxalate, phthalate, teraphthalate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, propiolate, propionate, phenylpropionate, salicylate, sebacate, succinate, suberate, sulfate, bisulfate, pyrosulfate, sulfite, bisulfite, sulfonate, benzene-sulfonate, p-bromophenylsulfonate, chlorobenzenesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, methanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, p-toluenesulfonate, xylenesulfonate, tartarate, salts and the like

[0056] A preferred salt of compounds of the present invention is the hydrochloride salt.

[0057] The pharmaceutically acceptable acid addition salts are typically formed by reacting a compound of formula I with one equivalent (or slight excess) of acid The reactants are generally combined in a mutual solvent such as diethyl ether, methanol, ethanol, or aqueous alcohol. The salt normally precipitates out of solution within about one hour to 10 days and can be isolated by filtration or the solvent can be stripped off by conventional means.

[0058] The pharmaceutically acceptable salts generally have enhanced solubility characteristics compared with the compound from which they are derived, and thus are often more amenable to formulation in solution or emulsion formulations.

[0059] For administration to a patient, the compounds of the present invention are formulated into a pharmaceutical formulation using standard practices well known in the formulation art. The present invention also provides pharmaceutical compositions which comprise compounds of the present invention formulated together with one or more non-toxic pharmaceutically acceptable carriers and/or excipients.

[0060] The formulations may be specially formulated for oral administration in solid or liquid form, for parenteral injection, or for rectal or vaginal administration by means of a suppository.

[0061] The pharmaceutical compositions of this invention can be administered to humans and other mammals orally, rectally, intravaginally, parenterally, topically (by means of powders, ointments, creams, or drops), bucally or sublingually, or as an oral or nasal spray. The term "parenteral administration" refers herein to modes of administration which include intravenous, intramuscular, intraperitoneal, instrasternal, subcutaneous, or intraarticular injection or infusion.

[0062] Pharmaceutical compositions of this invention for parenteral administration comprise sterile aqueous or non-aqueous solutions, dispersions, suspensions, or emulsions, as well as sterile powders which are reconstituted immediately prior to use into sterile solutions or suspensions. Examples of suitable sterile aqueous and non-aqueous carriers, diluents, solvents or vehicles include water, physiological saline solution, ethanol, polyols (such as glycerol, propylene glycol, poly(ethylene glycol), and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity is maintained, for example, by the use of coating materials such as lecithin, by the maintenance of proper particle size in the case of dispersions and suspensions, and by the use of surfactants.

[0063] Parenteral compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms is ensured by the inclusion of antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of injectable formulations may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin

[0064] In some cases, in order to prolong the effect of the drug, it is desirable to slow the absorption of the drug following subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension or crystalline or amorphous material of low water solubility or by dissolving or suspending the drug in an oil vehicle In the case of the subcutaneous or intramuscular injection of a suspension containing a form of the drug with low water solubility, the rate of absorption of the drug depends upon its rate of dissolution

[0065] Injectable "depot" formulations of the compounds of this invention are made by forming microencapsulated matrices of the drug in biodegradable polymers such as poly(lactic acid). poly(glycolic acid), copolymers of lactic and glycolic acid, poly (orthoesters), and poly (anhydrides) these materials which are described in the art. Depending upon the ratio of drug to polymer and the characteristics of the particular polymer employed, the rate of drug release can be

[0078] Generally, for the treatment of estrogen-related disorders, compounds of the present invention are administered at dosage levels between about 10 mg/kg of body weight and about 250 mg/kg of body weight per day If desired, the daily dosage may be divided into multiple doses for purposes of administration, e.g. into two to four doses per day.

[0079] The following Examples are provided in order to enable one skilled in the art to practice the present invention. However, the Examples are merely illustrative of the invention and are not to be read as limiting its scope which is defined by the appended claims

Preparation 1

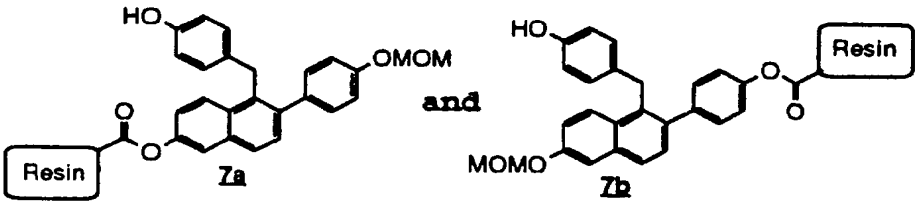
Preparation of acid chloride form of carboxypolystyrene resin

[0080] To a suspension of carboxypolystyrene resin (20.0 g, Novabiochem, La Jolla, California, 92039) in benzene (200 mL) under nitrogen atmosphere was added dropwise and excess (20 0 mL) of oxalyl chloride. The resulting mixture was heated to 70°C for 20 hours, then cooled to ambient temperature. Additional benzene (100 mL) was added to the mixture which was stirred for 5 minutes, and the resulting resin allowed to settle. The supernate was removed via cannula. This procedure was repeated 5 times using 200 ml benzene. After the final rinse, the resulting resin was dried under reduced pressure at 30°C until a constant mass (19 8 g) was obtained. Chlorine analysis showed the resin contained 8.09% Cl which corresponded to a new loading ratio of 2.29 mmol/g.

Preparation 2

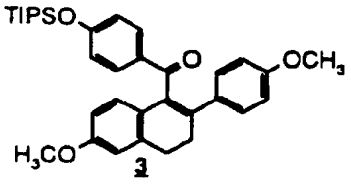
Preparation of a Mixture of the Resin-Bound Phenolic Substrates

[0081]



Step 1 - Preparation of 6-methoxy-2-(4-methoxyphenyl)-1-(4-triisopropylsilyloxybenzoyl)-3,4-dihydro-naphthalene

[0082]

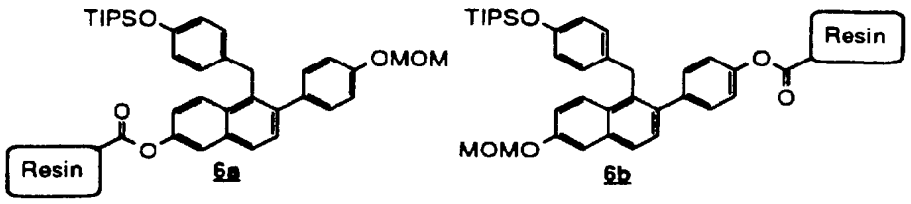


[0083] To a solution of 5.9 g (15.28 mmol) of 6-methoxy-2-(4-methoxyphenyl)-1-(4-hydroxybenzoyl)-3,4-dihydro-naphthalene (prepared as described in Jones, et al., J. Med. Chem , **35**. 931-938 (1992) in 200 mL of dichloromethane under a nitrogen atmosphere was added 1.87 g (15.28 mmol) of dimethylaminopyridine and 4.1 mL (15.28 mmol) of triisopropyl trifluoromethane-sulfonate ("TIPS triflate," Aldrich Chemical Co., Milwaukee, WI). The resulting mixture was stirred at room temperature for 48 hours, after which time the reaction was quenched by addition of aqueous sodium bicarbonate solution. The resulting mixture was extracted twice with dichloromethane. The organic layers were combined, extracted with brine solution, dried over anhydrous sodium sulfate and concentrated under vacuum to yield 8.05 g (97%) of the title compound as a thick yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$). δ Values: 1.06 (s, 9H), 1.19 (m, 1H), 2.79 (m, 2H), 3.01 (t, J = 7.7, 7.8, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 6 61-6.79 (m, 6H), 6.96 (d, J = 8.49, 1H), 7.17 (d, J = 6 8, 2H), and 7.73 (d, J = 7.13, 2H).

vacuum. Flash chromatograchy of the resulting oil on silica, eluting with dichloromethane yielded 1.37 g (45%) of a mixture of the two products as a yellow foam

Step 4 - Preparation of mixture of resin-bound 6-hydroxy-2-(4-methoxymethoxyphenyl)-1-(4-triisopropylsilyloxybenzoyl)naphthalene and 6-methoxymethoxy-2-(4-hydroxyphenyl)-1-(4-triisopropylsilyloxybenzoyl)naphthalene

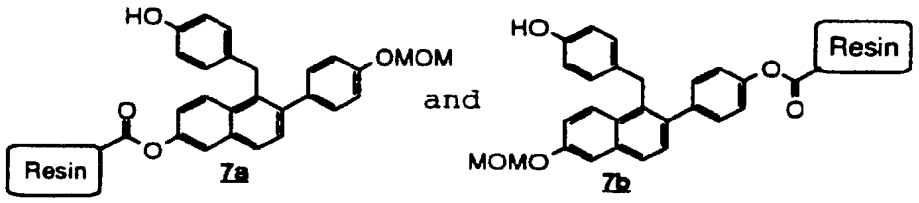
[0092]



[0093] To a solution in 25 mL of dichloromethane of 1 88 g (3.46 mmol) of the product mixture from step 3 were added, under nitrogen, 0.97 mL (6.92 mmol) of triethylamine and 1.51 g (3.46 mmol) of the resin in its acid chloride form (prepared as described in Preparation 1 above). The mixture was stirred gently at room temperature for 19 hours. After this time the reaction was quenched by the addition of 2 mL of methanol and the resulting mixture was stirred at room temperature for an additional 5 minutes. The reaction mixture was filtered and the filter residue was washed successively with 150 mL portions of dichloromethane, methanol, and dichloromethane to yield 2.95 g of the loaded resin with a loading ratio of 1.17 mmol/g

Step 5 - Preparation of the mixture of resin-bound 6-hydroxy-2-(4-methoxymethoxyphenyl)-1-(4-hydroxybenzyl) naphthalene and 6-methoxy-methoxy-2-(4-hydroxyphenyl)-1-(4-hydroxybenzyl)-naphthalene

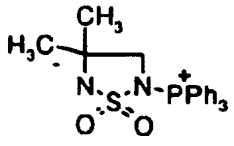
[0094]



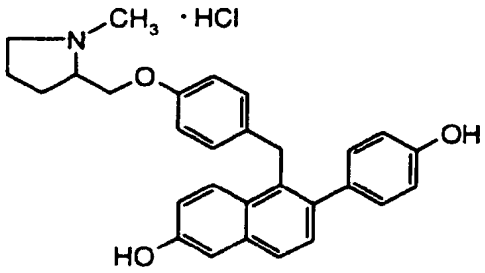
Preparation 3

Preparation of the Betaine Coupling Catalyst

[0095]



[0096] After the method of J. Castro, *et al*, J Org. Chem., **59**:2289-2291 (1994), to a stirred mixture of triphenylphosphine (8.73 g, 33.28 mmol) and 5.0 g (33.28 mmol) of 3,3-dimethyl-1,2,5-thiazolidine 1.1-dioxide in 100 mL of tetrahydrofuran under nitrogen were added, dropwise over a period of ten minutes, 5.25 mL (33 28 mmol) of diethylazodicarboxylate (DEAD) The resulting mixture was stirred at room temperature for 3 hours and the white solid pre-



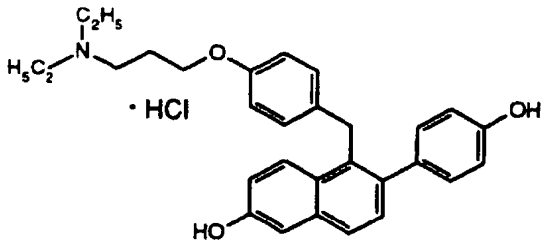
[0105] 6-Hydroxy-2-(4-hydroxyphenyl)-1-[4-(N-methylpyrrolidin-2-yl)methoxybenzyl]naphthalene hydrochloride

$C_{29}H_{29}NO_3$•HCl			
Mass	(Calc.)	439	(-HCl)
	(Found)	440	

Inhibition of MCF7 cell proliferation: ED_{50} = 0.5 nM

Example 2

[0106]



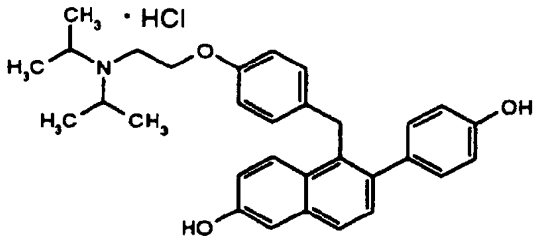
[0107] 6-Hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(N,N-diethylamino)propoxy)benzyl]naphthalene hydrochloride

$C_{28}H_{29}NO_3$•HCl			
Mass	(Calc.)	455	(-HCl)
	(Found)	456	

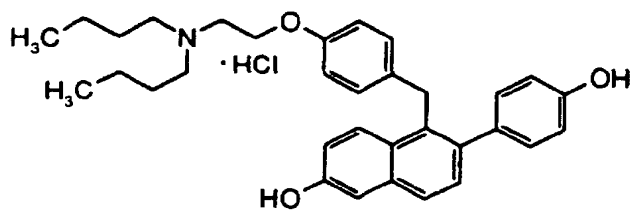
Inhibition of MCF7 cell proliferation: ED_{50} = 0.9 nM

Example 3

[0108]



[0109] 6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(N,N-diisopropylamino)ethoxy)benzyl]naphthalene hydrochloride

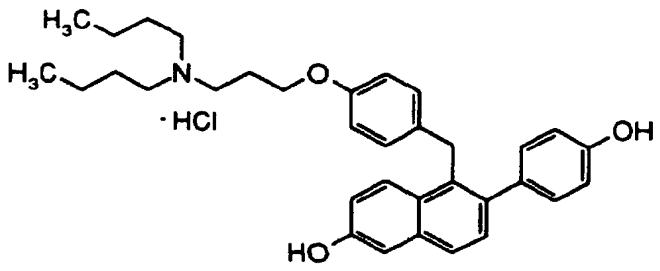


$C_{33}H_{39}NO_3$•HCl			
Mass	(Calc)	497	(-HCl)
	(Found)	498	

Inhibition of MCF7 cell proliferation: ED_{50} = 2 nM

Example 7

[0113] 6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(N,N-di-*n*-butylamino)propoxy)benzyl]naphthalene hydrochloride

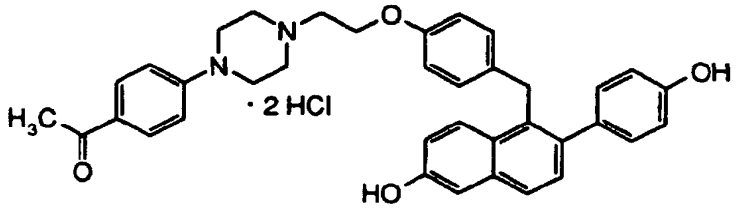


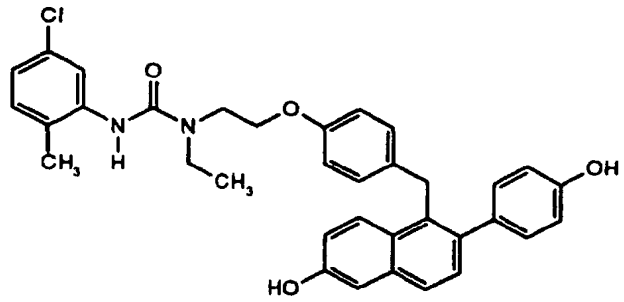
$C_{34}H_{41}NO_3$•HCl			
Mass	(Calc.)	511	(-HCl)
	(Found)	512	

Inhibition of MCF7 cell proliferation: ED_{50} = 4 nM

Example 8

[0114] 6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(4-(4-acetylphenyl)piperazin-1-yl)ethoxy)benzyl]naphthalene dihydrochloride



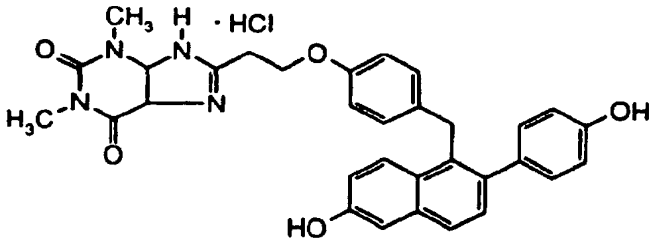


$C_{35}H_{33}ClN_2O_4$		
Mass	(Calc)	580
	(Found)	

Inhibition of MCF7 cell proliferation: ED_{50} = 10 nM

Example 12

[0118] 6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(2.3,5,6-tetrahydro-2,6-dioxo-1,3-dimethyl-1*H*-purin-8-yl)ethoxy) benzyl]naphthalene



$C_{32}H_{30}N_4O_5$		
Mass	(Calc)	550
	(Found)	548

Inhibition of MCF7 cell proliferation: ED_{50} = 20 nM

Example 13

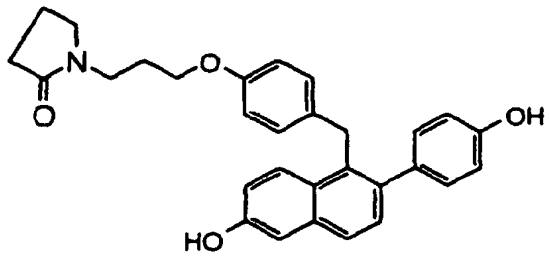
[0119] 6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(2,6-dimethylmorpholin-4-yl)ethoxy)benzyl]naphthalene hydrochloride

$C_{29}H_{27}NO_4$		
Mass	(Calc.)	453
	(Found)	454

Inhibition of MCF7 cell proliferation: ED_{50} = 40 nM

Example 16

[0122] 6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(pyrollidinon-1-yl)propoxy)benzyl]naphthalene



$C_{30}H_{29}NO_4$		
Mass	(Calc.)	467
	(Found)	468

Inhibition of MCF7 cell proliferation: ED_{50} = 30 nM

Biological Activity of the Compounds of the Present Invention - MCF-7 Proliferation Assay

[0123] The data reported in each of the Examples given above for inhibition of MCF-7 cell proliferation were obtained in an assay which determined each compound's ability to inhibit the proliferation of MCF-7 breast adenocarcinoma cells.

[0124] In the assay, these cells (ATCC HTB 22) are maintained in minimal essential medium, phenol red-free, (Sigma, St. Louis, MO) supplemented with 10% (V/V) fetal bovine serum (FBS), L-glutamine (2 mM), sodium pyruvate (1 mM), HEPES {(N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid] 10 mM), non-essential amino acids and bovine insulin (1 ug/mL) (maintenance medium). Ten days prior to assay, MCF-7 cells are switched to maintenance medium supplemented with 10% dextran coated charcoal stripped fetal bovine serum (DCC-FBS) assay medium) in place of 10% FBS to deplete internal stores of steroids. MCF-7 cells are removed from maintenance flasks using cell dissociation medium (Ca++/Mg++ free HBSS (phenol red-free) supplemented with 10 mM HEPES and 2 mM EDTA). Cells are washed twice with assay medium and adjusted to 80,000 cells/mL. Approximately 100 mL (8,000 cells) are added to flat-bottom microculture wells (Costar 3596) and incubated at 37° C in a 5% CO_2 humidified incubator for 48 hours to allow for cell adherence and equilibration after transfer. Serial dilutions of drugs or DMSO as a diluent control are prepared in assay medium and 50 mL transferred to triplicate microcultures followed by 50 mL assay medium for a final volume of 200 mL. After an additional 48 hours at 37° C in a 5% CO_2 humidified incubator, microcultures are pulsed with tritiated thymidine (1 uCi/well) for 4 hours Cultures are terminated by freezing at -70° C for 24 hours followed by thawing and harvesting of microcultures using a Skatron Semiautomatic Cell Harvester Samples are counted by liquid scintillation using a Wallac BetaPlace β counter. Activity of a compound of formula I in this present assay demonstrates that the compound is of potential value for treating hormonally-dependent cancer, particularly breast cancer.

Claims

1. A compound of the structure:

from the group consisting of

1-pyrrolidinyl,
1-piperidinyl,
1-azepinyl,
4-morpholinyl,
dimethyl-4-morpholinyl, and
N,N-dialkyl in which the alkyl groups are independently of one to four carbon atoms.

4. A compound as defined by Claim 3, or a pharmaceutically acceptable salt thereof,having the name

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(N-methylamino)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(N,N-dimethylamino)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(N-isopropylamino)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(N,N-diisopropylamino)methoxybenzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(N-isopropylamino)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(N-isopropylamino)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(N,N-diisopropylamino)propoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(N-butylamino)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(N,N-dibutylamino)propoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(N-methylamino)hexoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(N,N-dimethylamino)hexoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(N-ethylamino)hexoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(N,N-diethylamino)hexoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(N-isopropylamino)hexoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(N,N-diisopropylamino)hexoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(N-butylylamino)hexoxy)benzyl]naphthalene; or
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(6-(N,N-dibutylamino)hexoxy)benzyl]naphthalene.

5. A compound as defined by Claim 3, or a pharmaceutically acceptable salt thereof, having the name

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(pyrrolidin-1-yl)methoxybenzyl]naphthalene:
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(pyrrolidin-2-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(pyrrolidin-3-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(pyrrolidin-2-yl)ethoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(pyrrolidin-3-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(pyrrolidin-2-yl)propoxy)benzyl]naphthalene:
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(pyrrolidin-3-yl)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(pyrrolidin-1-yl)butoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(pyrrolidin-2-yl)butoxy)benzyl]naphthalene, or
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(pyrrolidin-3-yl)butoxy)benzyl]naphthalene.

6. A compound as defined by Claim 3, or a pharmaceutically acceptable salt thereof, having the name

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(piperidin-1-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(piperidin-2-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(N-methylpiperidin-2-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(piperidin-3-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(N-methylpiperidin-3-yl)methoxybenzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(piperidin-4-yl)methoxybenzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(piperidin-2-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(piperidin-3-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(piperidin-4-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(piperidin-2-yl)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(piperidin-3-yl)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(piperidin-4-yl)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(piperidin-1-yl)butoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(piperidin-2-yl)butoxy)benzyl]naphthalene,

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(2,3,5,6-tetrahydro-2,6-dioxo-1,3-dimethyl-1*H*-purin-8-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(2,3,5,6-tetrahydro-2,6-dioxo-1,3-dimethyl-1*H*-purin-8-yl)propoxy)benzyl]naphthalene. or
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(2,3.5,6-tetrahydro-2,6-dioxo-1,3-dimethyl-1*H*-purin-8-yl)butoxy)benzyl]naphthalene.

13. A compound as defined by Claim 1 or a pharmaceutically acceptable salt thereof wherein Z is 1,4-piperazinylene.

14. A compound as defined by Claim 14, or a pharmaceutically acceptable salt thereof, having the name

6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-phenylpiperazin-1-ylmethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(4-phenylpiperazin-1-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(4-phenylpiperazin-l-yl)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(4-phenylpiperazin-1-yl)butoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(4-methylphenyl)piperazin-1-ylmethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(4-chlorophenyl)piperazin-1-ylmethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(4-hydroxyphenyl)piperazin-l-ylmethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(4-methoxyphenyl)piperazin-1-ylmethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(4-(4-acetylphenyl)piperazin-1-ylmethoxy)benzyl]naphthalene.
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(4-(4-methylphenyl)piperazin-l-yl)ethoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(4-(4-chlorophenyl)piperazin-1-yl)ethoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(4-(4-hydroxyphenyl)piperazin-1-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(4-(4-methoxyphenyl)piperazin-1-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(2-(4-(4-acetylphenyl)piperazin-1-yl)ethoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(4-(4-methylphenyl)piperazin-1-yl)propoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(4-(4-chlorophenyl)piperazin-l-yl)propoxy)benzyl]naphthalene,
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(4-(4-hydroxyphenyl)piperazin-1-yl)propoxy)benzyl]naphthalene;
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(4-(4-methoxyphenyl)piperazin-l-yl)propoxy)benzyl]naphthalene, or
6-hydroxy-2-(4-hydroxyphenyl)-1-[4-(3-(4-(4-acetylphenyl)piperazin-1-yl)propoxy)benzyl]naphthalene.

15. A compound as defined by Claim 1 or a pharmaceutically acceptable salt thereof wherein Y is selected from ureido, N-(lower alkyl)ureido, N'-(lower alkyl)ureido, and N,N'-di(lower alkyl)ureido having the name

N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-phenyl urea,
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-phenyl urea;
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-phenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-methylphenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-chlorophenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-hydroxyphenyl urea,
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-methoxyphenyl urea;
N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-3-chloro-2-methylphenyl urea;
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-methylphenyl urea,
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-chlorophenyl urea;
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-hydroxyphenyl urea;
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-4-methoxyphenyl urea;
N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-3-chloro-2-methylphenyl urea;
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-methylphenyl urea,
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-phenyl urea,
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-chlorophenyl urea,
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-hydroxyphenyl urea;
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-4-methoxyphenyl urea; and
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-3-chloro-2-methylphenyl urea;
N-methyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-phenyl urea;
N-methyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenyl)ethyl]-N'-phenyl urea;
N-methyl-N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-phenyl urea;
N-methyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-methylphenyl urea;
N-methyl-N-[4-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylmethyl]-N'-4-chlorophenyl urea;

N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-ethyl-N'-phenyl urea;
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-ethyl-N'-4-chlorophenyl urea;
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'ethyl-N'-4-hydroxyphenyl urea;
N-[4-(3-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-ylmethyl)phenylpropyl]-N'-ethyl-N-4-methoxyphenyl urea:
or
N-ethyl-N-[4-(2-(6-hydroxy-2-(4-hydroxyphenyl)naphth-1-yl-methyl)phenoxy)ethyl]-N'-5-chloro-2-methylphenyl urea.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined by Claim 1 in combination with a pharmaceutically acceptable carrier.

17. A compound of formula I of Claim 1 for use as a medicament

18. A compound of formula I of Claim 1 for use in the prophylaxis or treatment of breast cancer.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 98 30 6198

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl 6)
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	11 November 1998	Juntunen, A

CATEGORY OF CITED DOCUMENTS

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